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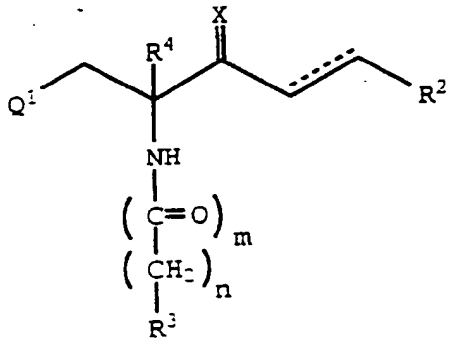
(54) 1-Aryl-2-acetylamidopentanone derivatives for use as tachykinin receptor antagonists

(57) This invention provides a novel series of the formula I substituted 1-aryl-2-acetamidopentanone derivatives which are useful in the treatment or prevention of a physiological disorder associated with an excess of tachykinins. This invention also provides methods for the treatment of such physiological disorders as well as pharmaceutical formulations which employ these novel compounds.



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Description

Tachykinins are a family of peptides which share the common amidated carboxy terminal sequence,

$$Phe\text{-}Xaa\text{-}Gly\text{-}Leu\text{-}Met\text{-}NH_2$$

hereinafter referred to as SEQ ID NO:1. Substance P was the first peptide of this family to be isolated, although its purification and the determination of its primary sequence did not occur until the early 1970's. Substance P has the following amino acid sequence,

$$Arg\text{-}Pro\text{-}Lys\text{-}Pro\text{-}Gln\text{-}Gln\text{-}Phe\text{-}Phe\text{-}Gly\text{-}Leu\text{-}Met\text{-}NH_2$$

hereinafter referred to as SEQ ID NO:2.

Between 1983 and 1984 several groups reported the isolation of two novel mammalian tachykinins, now termed neurokinin A (also known as substance K, neuromedin L, and neurokinin α), and neurokinin B (also known as neuromedin K and neurokinin β). See, J.E. Maggio, Peptides, 6 (Supplement 3):237-243 (1985) for a review of these discoveries. Neurokinin A has the following amino acid sequence,

$$His\text{-}Lys\text{-}Thr\text{-}Asp\text{-}Ser\text{-}Phe\text{-}Val\text{-}Gly\text{-}Leu\text{-}Met\text{-}NH_2$$

hereinafter referred to as SEQ ID NO:3. The structure of neurokinin B is the amino acid sequence,

$$Asp\text{-}Met\text{-}His\text{-}Asp\text{-}Phe\text{-}Phe\text{-}Val\text{-}Gly\text{-}Leu\text{-}Met\text{-}NH_2$$

hereinafter referred to as SEQ ID NO:4.

Tachykinins are widely distributed in both the central and peripheral nervous systems, are released from nerves, and exert a variety of biological actions, which, in most cases, depend upon activation of specific receptors expressed on the membrane of target cells. Tachykinins are also produced by a number of non-neural tissues.

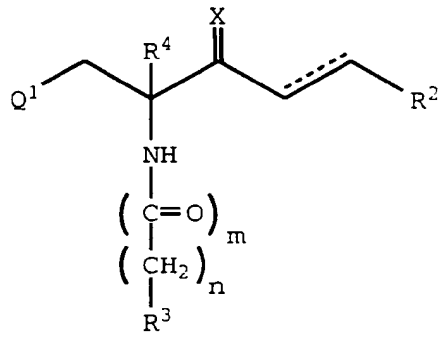
The mammalian tachykinins substance P, neurokinin A, and neurokinin B act through three major receptor subtypes, denoted as NK-1, NK-2, and NK-3, respectively. These receptors are present in a variety of organs.

Substance P is believed inter alia to be involved in the neurotransmission of pain sensations, including the pain associated with migraine headaches and with arthritis. These peptides have also been implicated in gastrointestinal disorders and diseases of the gastrointestinal tract such as inflammatory bowel disease. Tachykinins have also been implicated as playing a role in numerous other maladies, as discussed infra.

In view of the wide number of clinical maladies associated with an excess of tachykinins, the development of tachykinin receptor antagonists will serve to control these clinical conditions. The earliest tachykinin receptor antagonists were peptide derivatives. These antagonists proved to be of limited pharmaceutical utility because of their metabolic instability. Recent publications have described novel classes of non-peptidyl tachykinin receptor antagonists which generally have greater oral bioavailability and metabolic stability than the earlier classes of tachykinin receptor antagonists. Examples of such newer non-peptidyl tachykinin receptor antagonists are found in European Patent Publication 591, 040 A1, published April 6, 1994; Patent Cooperation Treaty publication WO 94/01402, published January 20, 1994; Patent Cooperation Treaty publication WO 94/04494, published March 3, 1994; and Patent Cooperation Treaty publication WO 93/011609, published January 21, 1993.

In essence, this invention provides a class of potent non-peptide tachykinin receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of known peptide-based tachykinin receptor antagonists.

This invention encompasses methods for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I



I

wherein:

Q^1 is phenyl, naphthyl, indolyl, benzothienyl, benzofuranyl, benzyl, or fluorenyl, any one of which may be substituted with halo, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^4 is hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

X is =O, =NOH or =NO(C_1-C_6 alkyl);

the dotted line indicates an optional covalent bond;

m is 0 or 1;

n is 0-6;

R^3 is hydrogen, trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, hexamethyleneiminyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, tetrahydropyridinyl, reduced quinolinyl, reduced isoquinolinyl, phenyl-(C_1-C_6 alkylidenyl)-, phenyl-(C_1-C_4 alkoxy)-, quinolinyl-(C_1-C_6 alkylidenyl)-, isoquinolinyl-(C_1-C_6 alkylidenyl)-, reduced quinolinyl-(C_1-C_6 alkylidenyl)-, reduced isoquinolinyl-(C_1-C_6 alkylidenyl)-, benzoyl-(C_1-C_6 alkylidenyl)-, C_1-C_4 alkyl, or -NH-CH_2-R^5;

any one of which R^3 groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

or any one of which R^3 groups may be substituted with phenyl, piperazinyl, C_3-C_8 cycloalkyl, benzyl, C_1-C_4 alkyl, piperidinyl, pyridinyl, pyrimidinyl, C_2-C_6 alkanoylamino, pyrrolidinyl, C_2-C_6 alkanoyl, or C_1-C_4 alkoxycarbonyl;

any one of which groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, or C_2-C_4 alkanoylamino;

or R^3 is amino, a leaving group, hydrogen, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

R^2 is phenyl, phenyl-(C_1-C_6 alkylidenyl)-, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_1-C_8 alkyl, naphthyl, C_2-C_8 alkenyl, or hydrogen;

any one of which groups except hydrogen may be substituted with one or two halo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, nitro, trifluoromethyl, or C_1-C_3 alkyl groups; and

R^5 is pyridyl, anilino-(C_1-C_6 alkylidenyl)-, or anilinocarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

In other embodiments this invention encompasses the novel compounds of Formula I and the salts and solvates of those compounds, as well as pharmaceutical formulations comprising at least one compound of Formula I, or a pharmaceutically acceptable salt or solvent of said compound, in combination with one or more pharmaceutically acceptable carrier, diluents, or excipients.

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "MS" refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As used herein, the term "C_1-C_6 alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C_1-C_6 alkyl" includes within its definition the terms "C_1-C_3 alkyl" and "C_1-C_4 alkyl".

"C_1-C_6 alkylidenyl" refers to a straight or branched, divalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, t-butylenyl, pentylenyl, isopentylenyl, and hexylenyl.

"Halo" represents chloro, fluoro, bromo or iodo.

"C_1-C_6 alkylthio" represents a straight or branched alkyl chain having from one to six carbon atoms attached to a sulfur atom. Typical C_1-C_6 alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio and the like. The term "C_1-C_6 alkylthio" includes within its definition the term "C_1-C_3 alkylthio".

The term "C_2-C_8 alkenyl" as used herein represents a straight or branched, monovalent, unsaturated aliphatic chain having from two to eight carbon atoms. Typical C_2-C_6 alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

"C_5-C_8 cycloalkenyl" represents a hydrocarbon ring structure containing from five to eight carbon atoms and having at least one double bond within that ring.

"C_1-C_6 alkylamino" represents a straight or branched alkylamino chain having from one to six carbon atoms attached to an amino group. Typical C_1-C_4 alkyl-amino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and the like. "C_1-C_6 alkylamino" encompasses within this term "C_1-C_4 alkylamino".

"Di(C_1-C_4 alkyl)amino" represents a straight or branched dialkylamino chain having two alkyl chains, each having independently from one to four carbon atoms attached to a common amino group. Typical di(C_1-C_4)alkylamino groups include dimethylamino, ethylmethylamino, methylisopropylamino, *t*-butylisopropylamino, di-*t*-butylamino and the like.

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the terms "C_1-C_3 alkoxy" and "C_1-C_4 alkoxy".

"C_2-C_6 alkanoyl" represents a straight or branched alkyl chain having from one to five carbon atoms attached to a carbonyl moiety. Typical C_2-C_6 alkanoyl groups include ethanoyl, propanoyl, isopropanoyl, butanoyl, *t*-butanoyl, pentanoyl, hexanoyl, 3-methylpentanoyl and the like.

"C_1-C_4 alkoxycarbonyl" represents a straight or branched alkoxy chain having from one to four carbon atoms attached to a carbonyl moiety. Typical C_1-C_4 alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, *t*-butoxycarbonyl and the like.

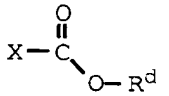
"C_3-C_8 cycloalkyl" represents a saturated hydrocarbon ring structure containing from three to eight carbon atoms. Typical C_3-C_8 cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxy-carbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is usually not critical so long as the derivatized amino group is stable to the condition of subsequent reactions on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting groups. Preferred amino-protecting groups are trityl, *t*-butoxycarbonyl (*t*-BOC), allyloxycarbonyl and benzyloxycarbonyl. Further examples of groups referred to by the above terms are described by E. Haslam, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (J.G.W. McOmie, ed., 1973), at Chapter 2; and T.W. Greene and P.G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, (1991), at Chapter 7.

The term "leaving group" as used herein refers to a group of atoms that is displaced from a carbon atom by the attack of a nucleophile in a nucleophilic substitution reaction. The term "leaving group" as used in this document encompasses, but is not limited to, activating groups.

The term "activating group" as used herein refers a leaving group which, when taken with the carbonyl (-C=O) group to which it is attached, is more likely to take part in an acylation reaction than would be the case if the group were not present, as in the free acid. Such activating groups are well-known to those skilled in the art and may be, for example, succinimidoxy, phthalimidoxy, benzotriazolyloxy, benzenesulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, azido, or -O-CO-(C_4-C_7 alkyl).

The term "haloformate" as used herein refers to an ester of a haloformic acid, this compound having the formula



wherein X is halo, and R^d is C_1-C_6 alkyl. Preferred haloformates are bromoformates and chloroformates. Especially preferred are chloroformates. Those haloformates wherein R^d is C_3-C_6 alkyl are preferred. Most preferred is isobutylchloroformate.

The compounds used in the method of the present invention may have one or more asymmetric centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the older D-L system is also used in this document to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix "D" is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

In order to preferentially prepare one optical isomer over its enantiomer, the skilled practitioner can proceed by one of two routes. The practitioner may first prepare the mixture of enantiomers and then separate the two enantiomers. A commonly employed method for the resolution of the racemic mixture (or mixture of enantiomers) into the individual enantiomers is to first convert the enantiomers to diastereomers by way of forming a salt with an optically active acid or base. These diastereomers can then be separated using differential solubility, fractional crystallization, chromatography, or like methods. Further details regarding resolution of enantiomeric mixtures can be found in J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", (1991).

In addition to the schemes described above, the practitioner of this invention may also choose an enantiospecific protocol for the preparation of the compounds of Formula I. Such a protocol employs a synthetic reaction design which maintains the chiral center present in the starting material in a desired orientation. These reaction schemes usually produce compounds in which greater than 95 percent of the title product is the desired enantiomer.

In addition to the (R)-(S) system of stereochemistry, those compounds of Formula I in which the optional double bond is present also have the capacity for (E)-(Z) isomerism. In this system the group of higher priority bonded to one of the carbon atoms sharing the double bond is compared to the group of higher priority bonded to the other carbon atom sharing the double bond. If the two groups of higher priority are on the same side of the double bond, the alkene is designated (Z) (*zusammen*). If the two groups of higher priority are on opposite sides of the double bond the alkene is designated (E) (*entgegen*). As noted supra, all asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

As noted supra, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycolate, tartrate,

methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formulas I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

This invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of Formula I. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other in vivo processes to the parent bioactive form. This prodrug should have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation or solubility, or improved systemic stability (an increase in plasma half-life, for example).

Typically, such chemical modifications include:

1) ester or amide derivatives which may be cleaved by esterases or lipases;

2) peptides which may be recognized by specific or nonspecific proteases; or

3) derivatives that accumulate at a site of action through membrane selection of a prodrug form or a modified prodrug form;

or any combination of 1 to 3, supra. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H, Bundgaard, Design of Prodrugs, (1985).

The especially preferred methods of this invention are those methods employing compounds wherein:

a) Q^1 is phenyl, 3-indolyl, optionally substituted with one or two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, chloro, fluoro, and trifluoromethyl;

b) the double bond is absent;

c) R^3 is phenyl, substituted phenyl, piperidinyl, substituted piperidinyl, piperazinyl, substituted piperazinyl, pyrrolidinyl, substituted pyrrolidinyl, pyridyl, benzoyl, or morpholinyl;

d) R^2 is phenyl, substituted phenyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, naphthyl or substituted naphthyl;

e) n is 1;

f) m is 1; and

g) R^4 is hydrogen.

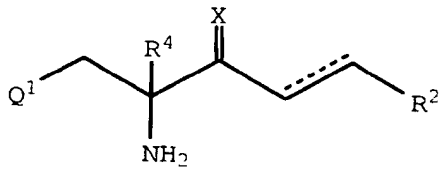
A most preferred group of compounds used in the methods of this invention are those of Formula I wherein Q^1 is unsubstituted phenyl or 3-indolyl, R^3 is substituted piperidinyl or substituted piperazinyl, and R^2 is mono- or disubstituted phenyl.

The compounds of the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

The term "optionally in the presence of a base" indicates that the reaction may be performed with a base present, but such a base is not required for the reaction to proceed. Preferred bases include organic bases containing one or

more nitrogen groups, such as N-methylmorpholine, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, pyridine, and the like. Especially preferred are N-methylmorpholine and pyridine. The absence of a base is usually most preferred.

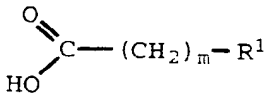
A preferred process for preparing the compounds of Formula I where m is 1 is by the acylation of the primary amine of a compound of Formula II



or a salt or solvate thereof.

The acylation of this primary amine can be accomplished by a number of methods known in the art. The primary amine can be selectively acylated by various means. This acylation can be done using any of a large number of techniques regularly employed by those skilled in organic chemistry. One such reaction scheme is a substitution using an anhydride such as acetic anhydride or another activated carboxylate, such as a carboxylic acid halide.

Another preferred reaction scheme often employed to acylate a primary amine employs a carboxylic acid of Formula III

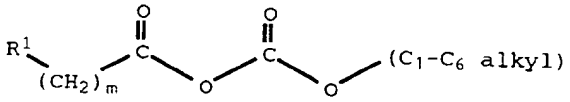


III

or a salt or solvate thereof, preferably with an activating agent, such as 1,1-carbonyl diimidazole, dicyclohexylcarbodiimide, diethyl azodicarboxylate, 1-hydroxybenzotriazole, alkyl chloroformate and triethylamine, phenyldichlorophosphate, and chlorosulfonyl isocyanate.

An amino-de-alkoxylation type of reaction uses esters as a means of acylating the primary amine. Activated esters which are attenuated to provide enhanced selectivity are very efficient acylating agents.

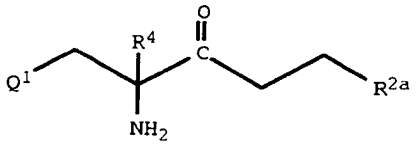
In an especially preferred embodiment, a compound of Formula III, or a salt thereof, is first reacted with a suitable haloformate, forming the mixed anhydride of Formula IIIa.



IIIa

This intermediate is then reacted with a compound of Formula II, or a salt thereof, optionally in the presence of a base.

The intermediates of Formula II are generally prepared essentially as described in Patent Cooperation Treaty published application WO 94/01402, published January 20, 1994. Those intermediates of Formula II wherein X is =O and the double bond is present may be prepared by reaction of an aldehyde of formula R^2CHO with a compound of Formula IIa



IIa

wherein Q^1 and R^4 are a previously defined and R^{2a} represents a group PR^x_3 or $PO(OR^x)_2$, wherein R^x represents phenyl or C_1-C_6 alkyl, in the presence of a suitable base.

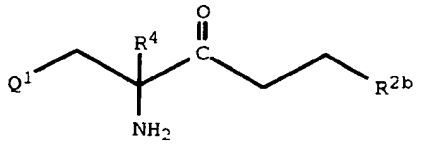
Suitable bases include alkali metal hydrides, such as, for example, sodium hydride, alkali metal carbonatews, such as, for example, potassium carbonate, and strong organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene in the presence of anhydrous lithium chloride. The reaction is conveniently effected in a suitable organic solvent, such as an ether like tetrahydrofuran, or acetonitrile, suitably at ambient temperature.

Those intermediates of Formula II in which X is =NOH or =NO(C_1-C_6 alkyl) may be prepared from the corresponding compounds of Formula II wherein X is =O by the addition of hydroxylamine, or a derivative thereof. Compounds wherein X is =NO(C_1-C_6 alkyl) may be prepared from the corresponding compounds wherein X is =NOH by alkylation, for example, using a diazocompound, such as diazomethane, or an alkyl halide or sulfate.

Compounds of Formula II wherein the double bond is absent may be prepared from the corresponding unsaturated compound of Formula II by reduction. Suitable reduction procedures include catalytic hydrogenation. Suitable hydrogenation catalysts include nobel metals, for example, platinum or palladium, or oxides thereof, which may be supported, for example, on charcoal. A preferred catalyst is Wilinson's catalyst tris(triphenylphospine)rhodium(I)chloride,

This reduction is conveniently performed in a suitable organic solvent, such as an ether like tetrahydrofuran, an alcohol like ethanol, or an ester like ethyl acetate, suitably at ambient temperature.

Compounds of Formula IIa may be prepared from compounds of Formula IIb



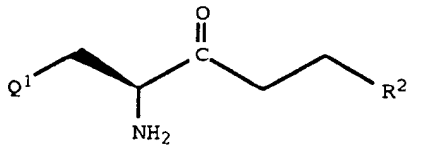
IIb

wherein R^{2b} represents C_1-C_6 alkoxy, or a suitably substituted amino group, such as NR^yOR^z, where R^y and R^z independently represent C_1-C_6 alkyl, in particular $NCH_3(OCH_3)$, by reaction with a compound having the formula $CH_3PO(OR^{2x})_2$, where R^{2x} is C_1-C_6 alkyl, in the presence of a base.

Suitable reaction procedures will be readily apparent to the skilled practitioner and examples thereof are described in the accompanying Preparations and Examples. Suitable bases of use in the reaction include alkyl lithiums, such as butyl lithium.

Compounds of Formula IIb are commercially available or may be preapred using standard procedures well known to the skilled person in the art. The compounds of Formula IIb are amino acid derivatives. Syntheses of amino acids and derivatives thereof are well documented and well described. See, e.g., "Chemistry and Biochemistry of the Amino Acids", (G.C. Barrett, ed., Chapman and Hall, 1985).

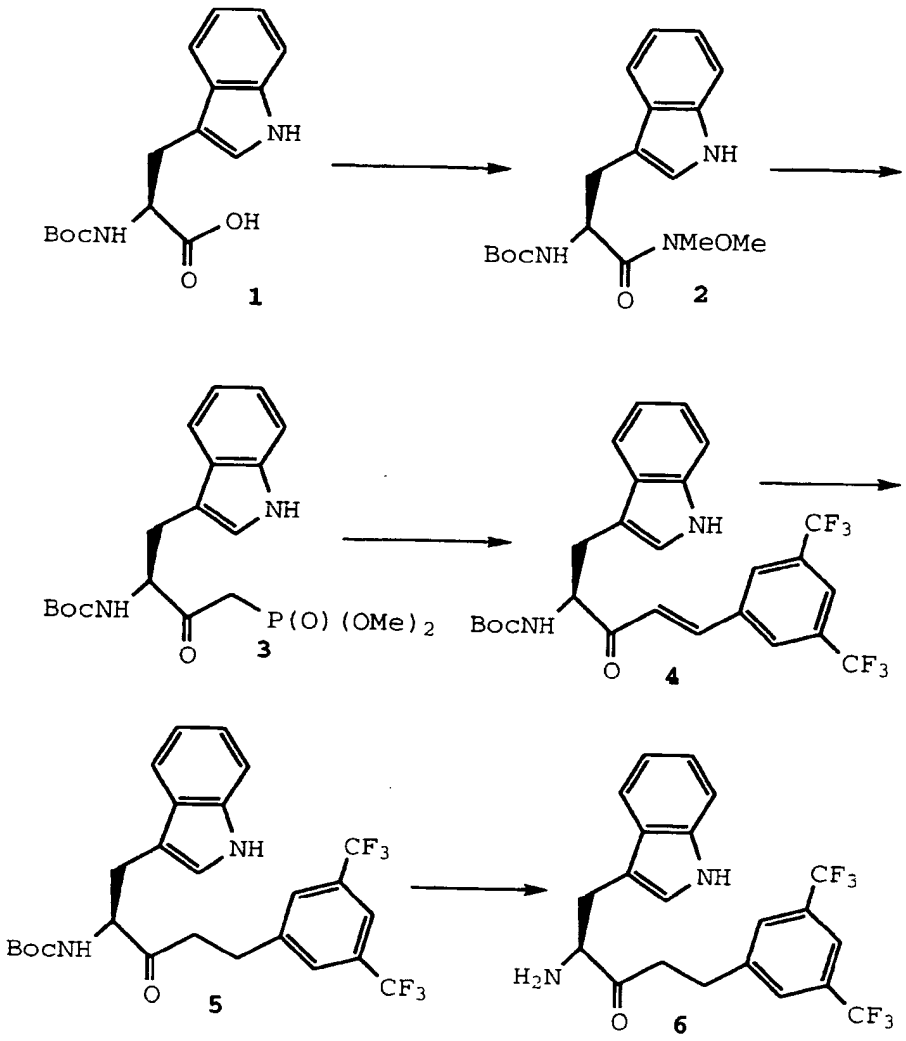
As noted supra, many of the the compounds of Formula I may be prepared as individual enantiomers. Especially preferred are those compounds which are derivatives of a compound of Formula IIc



IIc

The compounds of Formula IIc are prepared essentially as described in K.J. Merchant, et al., Tetrahedron Letters, 35:4205-4208 (1994). These compounds are prepared in an enantioselective manner. One example of such a synthesis is depicted in Scheme I, infra.

Scheme I

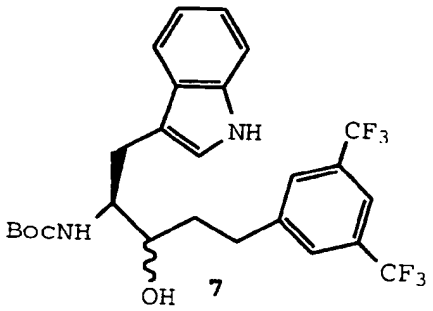


"Boc" refers to the radical formed by protecting the amino group with *t*-butoxycarbonyl.

In the reactions depicted in this scheme the N-α-Boc-tryptophan (**1**) is used to prepared the corresponding Weinreab amide (**2**). S. Natham and S.M. Weinreb, Tetrahedron Letters, 22:3815 (1981). The amide is usually formed by reacting the protected amino acid with N,O-dimethylhydroxylamine hydrochloride and an alkyl haloformate in a suitably non-reactive solvent, such as N,N-diethylformamide.

The reaction of (**2**) with the phosphonate anion to give (**3**) must be done at very low reaction temperatures in order to avoid racemization. Typically, lithio dimethylmethylphosphonate is pre-cooled to about -78°C in a solvent such as tetrahydrofuran before it is added to (**2**), which has also been pre-cooled to about -78°C. This addition is performed very slowly so as to maintain enantiomeric purity.

The resulting phosphonate (**3**) may be purified by chromatography, but more preferably is used in the subsequent steps without further purification. The phosphonate (**3**) is then reacted with a substituted benzaldehyde to yield the unsaturated ketone (**4**). This reaction is generally performed by stirring in acetonitrile with potassium carbonate to yield the unsaturated ketone (**4**), the double bond of which may then be reduced by hydrogenation using palladium on charcoal as a catalyst to yield the corresponding amino ketone (**5**). Over-reduction of (**4**) may yield the corresponding saturating alcohol (**7**), which can be separated from (**5**) by chromatography.



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Heating of (**4**) with one equivalent of tributyl tin hydride in toluene for 16 hours results in greater than 76% yield of (**5**), but chromatography is still required to remove tin residues. Hydrogenation of (**4**) using freshly prepared Wilkinson's catalyst gives clean reduction to the saturated amino ketone (>95%).

The amino ketone (**5**) is then deprotected using standard techniques to yield a compound of Formula II (**6**). Especially preferred is the use of dry gaseous hydrogen chloride in a suitable solvent, such as dry ethyl ether.

During any of the above synthetic sequences it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of protecting groups described, supra.

The following non-limiting Preparations and Examples illustrate the preparation of compounds according to the invention.

Preparation 1

Synthesis of 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

(a) N-methoxy-N-methyl-2-*t*-butoxycarbonylamino-3-(3-indolyl)propionamide

N-*t*-BOC-tryptophan (100 g) is dissolved in N,N-dimethylformamide (800 ml) and triethylamine (101 g) is added. The reaction mixture is cooled to -30°C and isobutyl chloroformate (42.5 ml) is added, the internal temperature being maintained below -20°C. The resulting reaction mixture is stirred for about 15 minutes before adding N,O-dimethyl hydroxylamine hydrochloride (64 g) and the diluting the reactin mixture with dichloromethane (1 L), the reaction mixture being maintained below 0°C. The reaction is stirred for 15 minutes, poured into ethyl acetate (3 L) and washed with 10% citric acid (1 L), water (3 x 1L), saturated sodium bicarbonate (1 L) and water (1 L). The organic phase is dried over magnesium sulfate, filtered, and evaporated until crystallization ensued. The suspension is diluted with petroleum ether, filtered, and dried to yield the title intermediate.

(b) 2-*t*-butoxycarbonylamino-1-(3-indolyl)-4-dimethylphosphone-3-butanone

Dimethyl methane phosphonate (205 g) is dissolved in tetrahydrofuran (800 ml), cooled to -70°C; and then treated with *n*-butyllithium (1.6 M in hexanes, 900 ml), the reaction temperature being maintained below -55°C. The reaction mixture is stirred for one hour before adding the product of part (a) (90 g). The resulting mixture is stirred at -70°C for about 30 minutes before quenching with saturated ammonium chloride. The resulting mixture is extracted with ethyl acetate and the organic extract is washed with water (5 x 500 ml), dried over magnesium sulfate, and evaporated. The residue is further purified on silica (eluting with ethyl acetate) to yield the title intermediate as an oil.

(c) 5-(3,5-ditrifluoromethylphenyl)-2-*t*-butoxycarbonylamino-1-(3-indolyl)-pent-4-en-3-one

A solution of the product of part (b) (69.0 g) in acetonitrile (600 ml) is stirred with diisopropylethylamine (43.3 g), and anhydrous lithium chloride (14.13 g) for 30 minutes before adding 3,5-ditrifluoromethylbenzaldehyde (55 g) in acetonitrile (200 ml). The reaction is stirred for two hours and then the solvent is removed and the residue is partitioned between ethyl acetate and water. The organic phase is washed with 10% citric acid (50 ml), water (500 ml), saturated sodium bicarbonate (500 ml), and water (500 ml). The solution is dried over magnesium sulfate, filtered, and evaporated. The residue is further purified by chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title intermediate as a pale yellow solid.

(d) 5-(3,5-ditrifluoromethylphenyl)-2-*t*-butoxycarbonylamino-1-(3-indolyl)-3-pentanone

The product of part (c) is heated under reflux with tri-n-butyltin hydride (51.12 g) in toluene for about 20 hours. The reaction is cooled and purified by column chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title intermediate as a white solid.

(e) 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The product of part (d) is treated with ethereal hydrogen chloride for about one hour. The precipitated white solid is filtered and dried to yield the title intermediate.

Preparation 2

Synthesis of 2-amino-5-(3,5-dimethoxyphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 3,5-dimethoxybenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 3

Synthesis of 2-amino-5-(3,5-dimethylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 3,5-dimethylbenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 4

Synthesis of 2-amino-5-(3,5-dichlorophenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 3,5-dichlorobenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 5

Synthesis of 2-amino-5-(2-trifluoromethylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 2-trifluoromethylbenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 6

Synthesis of 2-amino-5-(2-methoxyphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 2-methoxybenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 7

Synthesis of 2-amino-5-(2-methylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 2-methylbenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 8

Synthesis of 2-amino-5-(2-chlorophenyl)-1-(3-indolyl)-3-pentanone hydrochloride

The title intermediate is prepared essentially as described in Preparation 1 except that 2-chlorobenzaldehyde is employed instead of 3,5-ditrifluoromethylbenzaldehyde in step (c).

Preparation 9

Synthesis of 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3-benzo[b]thienyl)-3-pentanone

(a) 3-(3-benzo[b]thienyl)-2-*t*-butoxycarbonylamino propionic acid

2-Amino-3-(3-benzo[b]thienyl)propionic acid, prepared as described in International Journal of Peptide and Protein Research, 29:118 (1987), (22.9 g) and sodium carbonate (27.6 g) are added to a mixture of water (350 ml) and 1,4-dioxane (150 ml). Di-*t*-butyldicarbonate (34.1 g) is added to the mixture and the reaction is stirred for about 16 hours and washed with ether (500 ml). The reaction mixture is acidified to pH 3.0 with solid citric acid and extracted with ethyl acetate to yield the title intermediate.

(b) 2-Amino-5-(3,5-ditrifluoromethyl)-1-(3-benzo[b]thienyl)-3-pentanone

The title intermediate is prepared essentially as described in Preparations 1(b)-(e), starting with the compound of Preparation 9(a) instead of the compound of Preparation 1(a).

Preparation 10

Synthesis of 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3,4-dichlorophenyl)-3-pentanone

The title intermediate is prepared essentially as described in Preparation 9 starting with 3,4-dichlorophenylalanine.

Preparation 11

Synthesis of 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3-benzofuryl)-3-pentanone

The title compound is prepared essentially as described in Preparation 9 except that 2-amino-3-(3-benzofuryl)propionic acid is employed instead of 2-amino-3-(3-benzo[b]thienyl)propionic acid. The 2-amino-3-(3-benzofuryl)propionic acid is prepared essentially as described in International Journal of Peptide and Protein Research, supra, except that benzofuran is employed as the base substrate in place of the benzo[b]thiophene.

Preparation 12

Preparation of 2-((4-cyclohexyl)piperazin-1-yl)acetic acid potassium salt hydrate

Cyclohexylpiperazine (10.0 g, 0.059 mol) is added to ten volumes of methylene chloride at room temperature. To this mixture is added sodium hydroxide (36 ml of a 2N solution, 0.072 mol) and tetrabutylammonium bromide (1.3 g, 0.004 mol). After the addition of the sodium hydroxide and tetrabutylammonium bromide, methyl bromoacetate (7.0 ml, 0.073 mol) is added and the reaction mixture is stirred for four to six hours. The progress of the reaction is monitored by gas chromatography.

The organic fraction is separated and the aqueous phase is back-extracted with methylene chloride. The organic phases are combined and washed twice with deionized water, once with saturated sodium bicarbonate solution, and then with brine. The organic phase is dried over magnesium sulfate and the solvents are removed in vacuo to yield 2-((4-cyclohexyl)piperazin-1-yl)methyl acetate as a yellowish oil.

The title intermediate is prepared by dissolving the 2-((4-cyclohexyl)piperazin-1-yl)methyl acetate (10.0 g, 0.042 mol) in ten volumes of diethyl ether. This solution is cooled to 15°C and then potassium trimethylsilanoate (5.9 g, 0.044) is added. This mixture is then stirred for four to six hours. The reaction product is removed by filtration, washed twice with five volumes of diethyl ether, then washed twice with five volumes of hexanes, and then dried in a vacuum oven for 12-24 hours at 50°C.

Preparation 13

Preparation of 2-(4-(piperidin-1-yl)piperidin-1-yl)acetic acid, potassium salt

4-Piperidinylpiperidine (1.20 kg, 7.13 mol) is added to methylene chloride (12.0 L) under a nitrogen atmosphere. Tetrabutylammonium bromide (0.150 kg, 0.47 mol) and sodium hydroxide (1.7 L of a 5 N solution, 8.5 mol) are then added. The reaction mixture is cooled to 10-15°C and methyl bromoacetate (1.17 kg, 7.65 mol) is added and the resulting mixture is stirred for a minimum of 16 hours.

Deionized water (1.2 L) is then added to the mixture and the layers separated. The aqueous layer is back-extracted with methylene chloride (2.4 L). The organic fractions are combined and washed with deionized water (3 x 1.2 L), a saturated sodium bicarbonate solution (1.1 L) and a saturated sodium chloride solution (1.1 L). The organic fraction is then dried over anhydrous magnesium sulfate and concentrated to an oil on a rotary evaporator to yield 2-(4-(piperidin-1-yl)piperidin-1-yl)methyl acetate.

A solution of 2-(4-(piperidin-1-yl)piperidin-1-yl)methyl acetate (2.395 kg, 9.96 mol) in methanol (2.4 L) is added to a solution of potassium hydroxide (0.662 kg, 10.0 mol @ 85% purity) in methanol (10.5 L) under a nitrogen atmosphere. The reaction mixture is heated to 45-50°C for a minimum of 16 hours.

A solvent exchange from methanol to acetone (15.0 L) is performed on the solution on a rotary evaporator. This solution is slowly cooled to room temperature over 16 hours. The resulting solids are filtered, rinsed with acetone (5.0 L) and then dried to yield 2.471 kg (92%) of 2-(4-(piperidin-1-yl)piperidin-1-yl)acetic acid, potassium salt.

Example 1

Preparation of 2-[2-[(4-cyclohexyl)piperazin-1-yl]acetylamino-5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone

The title compound is prepared by first cooling 2-((4-cyclohexyl)piperazin-1-yl)acetic acid potassium salt to a temperature between -8°C and -15°C in 5 volumes of anhydrous methylene chloride. To this mixture is added isobutylchlo-

roformate at a rate such that the temperature does not exceed -8°C. The resulting reaction mixture is stirred for about 1 hour, the temperature being maintained between -8°C and -15°C.

To this mixture is then added 2-amino-5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone hydrochloride at such a rate that the temperature does not exceed 0°C. Next added to this mixture is N-methyl morpholine at a rate such that the temperature does not exceed 0°C. This mixture is then stirred for about 1 hour at a temperature between -15°C and -8°C.

The reaction is quenched by the addition of 5 volumes of water. The organic layer is washed once with a saturated sodium bicarbonate solution. The organic phase is then dried over anhydrous potassium carbonate and filtered to remove the drying agent. To the filtrate is then added 2 equivalents of concentrated hydrochloric acid, followed by 1 volume of isopropyl alcohol. The methylene chloride is then exchanged with isopropyl alcohol under vacuum by distillation.

The final volume of isopropyl alcohol is then concentrated to three volumes by vacuum. The reaction mixture is cooled to 20°C to 25°C and the product is allowed to crystallize for at least one hour. The desired product is then recovered by filtration and washed with sufficient isopropyl alcohol to give a colorless filtrate. The crystal cake is then dried under vacuum at 50°C.

Example 2

Preparation of 5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-2-[2-[(4-phenyl)piperazin-1-yl]acetylamino-3-pentanone

The title compound is prepared essentially as described in Example 1, except that 2-((4-phenyl)piperazin-1-yl)acetic acid, sodium salt is employed instead of 2-((4-cyclohexyl)piperazin-1-yl)acetic acid potassium salt.

Example 3

Preparation of 5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-2-[2-[(4-(piperidin-1-yl)piperidin-1-yl]acetyl]amino-3-pentanone

The title compound is prepared essentially as described in Example 1, except that 2-[4-(piperidin-1-yl)piperidin-1-yl] acetic acid, sodium salt is employed instead of 2-((4-cyclohexyl)piperazin-1-yl)acetic acid potassium salt.

Example 4

Preparation of 5-(3,5-ditrifluoromethylphenyl)-1-(3-indolyl)-2-[2-[(4-(piperidin-1-yl)piperidin-1-yl] acetyl] amino-3-oximinopentane

The compound of Example 3 (1.0 g) in methanol (20 ml) is treated with hydroxylamine hydrochloride (0.5 g) and sodium acetate (1.5 g) for 16 hours. The solution is concentrated in vacuo and the residue is partitioned between ethyl acetate and water. The ethyl acetate solution is separated, dried, and concentrated and the residue is crystallized from ethyl acetate/petroleum ether to give the title compound.

The biological activity of the compounds of the present invention is evaluated employing an initial screening assay which rapidly and accurately measured the binding of the tested compound to known NK-1 and NK-2 receptor sites. Assays useful for evaluating tachykinin receptor antagonists are well known in the art. See, e.g., J. Jukic, et al., Life Sciences, 49:1463-1469 (1991); N. Kucharczyk, et al., Journal of Medicinal Chemistry, 36:1654-1661 (1993); N. Rouissi, et al., Biochemical and Biophysical Research Communications, 176:894-901 (1991).

NK-1 Receptor Binding Assay

Radioreceptor binding assays are performed using a derivative of a previously published protocol. D.G. Payan, et al., Journal of Immunology, 133:3260-3265 (1984). In this assay an aliquot of IM9 cells (1×10^6 cells/tube in RPMI 1604 medium supplemented with 10% fetal calf serum) is incubated with 20 pM ^{125}I-labeled substance P in the presence of increasing competitor concentrations for 45 minutes at 4°C.

The IM9 cell line is a well-characterized cell line which is readily available to the public. See, e.g., Annals of the New York Academy of Science, 190: 221-234 (1972); Nature (London), 251:443-444 (1974); Proceedings of the National Academy of Sciences (USA), 71:84-88 (1974). These cells are routinely cultured in RPMI 1640 supplemented with 50 µg/ml gentamicin sulfate and 10% fetal calf serum.

The reaction is terminated by filtration through a glass fiber filter harvesting system using filters previously soaked for 20 minutes in 0.1% polyethylenimine. Specific binding of labeled substance P is determined in the presence of 20 nM unlabeled ligand.

Many of the compounds employed in the methods of the present invention are also effective antagonists of the NK-2 receptor.

NK-2 Receptor Binding Assay

The CHO-hNK-2R cells, a CHO-derived cell line transformed with the human NK-2 receptor, expressing about 400,000 such receptors per cell, are grown in 75 cm^2 flasks or roller bottles in minimal essential medium (alpha modification) with 10% fetal bovine serum. The gene sequence of the human NK-2 receptor is given in N.P. Gerard, et al., Journal of Biological Chemistry, 265:20455-20462 (1990).

For preparation of membranes, 30 confluent roller bottle cultures are dissociated by washing each roller bottle with 10 ml of Dulbecco's phosphate buffered saline (PBS) without calcium and magnesium, followed by addition of 10 ml of enzyme-free cell dissociation solution (PBS-based, from Specialty Media, Inc.). After an additional 15 minutes, the dissociated cells are pooled and centrifuged at 1,000 RPM for 10 minutes in a clinical centrifuge. Membranes are prepared by homogenization of the cell pellets in 300 ml 50 mM Tris buffer, pH 7.4 with a Tekmar® homogenizer for 10-15 seconds, followed by centrifugation at 12,000 RPM (20,000 x g) for 30 minutes using a Beckman JA-14® rotor. The pellets are washed once using the above procedure. and the final pellets are resuspended in 100-120 ml 50 mM Tris buffer, pH 7.4, and 4 ml aliquots stored frozen at -70°C. The protein concentration of this preparation is 2 mg/ml.

For the receptor binding assay, one 4-ml aliquot of the CHO-hNK-2R membrane preparation is suspended in 40 ml of assay buffer containing 50 mM Tris, pH 7.4, 3 mM manganese chloride, 0.02% bovine serum albumin (BSA) and 4 µg/ml chymostatin. A 200 µl volume of the homogenate (40 µg protein) is used per sample. The radioactive ligand is [^{125}I]iodohistidyl-neurokinin A (New England Nuclear, NEX-252), 2200 Ci/mmol. The ligand is prepared in assay buffer at 20 nCi per 100 µl; the final concentration in the assay is 20 pM. Non-specific binding is determined using 1 µM eledoisin. Ten concentrations of eledoisin from 0.1 to 1000 nM are used for a standard concentration-response curve.

All samples and standards are added to the incubation in 10 µl dimethylsulfoxide (DMSO) for screening (single dose) or in 5 µl DMSO for IC_{50} determinations. The order of additions for incubation is 190 or 195 µl assay buffer, 200 µl homogenate, 10 or 5 µl sample in DMSO, 100 µl radioactive ligand. The samples are incubated 1 hour at room temperature and then filtered on a cell harvester through filters which had been presoaked for two hours in 50 mM Tris buffer, pH 7.7, containing 0.5% BSA. The filter is washed 3 times with approximately 3 ml of cold 50 mM Tris buffer, pH 7.7. The filter circles are then punched into 12 x 75 mm polystyrene tubes and counted in a gamma counter.

Since the compounds of Formula I are effective tachykinin receptor antagonists, these compounds are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of tachykinins" encompasses those disorders associated with an inappropriate stimulation of tachykinin receptors, regardless of the actual amount of tachykinin present in the locale.

These physiological disorders may include disorders of the central nervous system such as anxiety, depression, psychosis, and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer's type, Alzheimer's disease, AIDS-associated dementia, and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as peripheral neuropathy, such as diabetic and chemotherapy-induced neuropathy, and post-herpetic and other neuralgias; acute and chronic obstructive airway diseases such as adult respiratory distress syndrome, bronchopneumonia, bronchospasm, chronic bronchitis, drivercough, and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, and rheumatoid arthritis; disorders of the musculo-skeletal system, such as osteoporosis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatites; addiction disorders such as alcoholism; stress-related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal disorders or diseases associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, emesis, and irritable bowel syndrome; disorders of bladder function such as bladder detrusor hyper-reflexia and incontinence; artherosclerosis; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; irritative symptoms of benign prostatic hypertrophy; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine, and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. For example the compounds of Formula I may suitably be used in the treatment of disorders of the central nervous system such as anxiety, psychosis, and schizophrenia; neurodegenerative disorders such as Alzheimer's disease and Down's syndrome; respiratory diseases such as bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological disorders such as rejection of transplanted tissues; gastrointestinal disorders and diseases such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, emesis, and irritable bowel syndrome; incontinence; disorders of blood flow caused by vasodi-

lation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

Many of the compounds of Formula I are selective tachykinin receptor antagonists. These compounds preferentially bind one tachykinin receptor subtype compared to other such receptors. Such compounds are especially preferred.

For example, NK-1 antagonists are most especially preferred in the treatment of pain, especially chronic pain, such as neuropathic pain, post-operative pain, and migraines, pain associated with arthritis, cancer-associated pain, chronic lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunbum, post partum pain, angina pain, and genitourinary tract-related pain including cystitis.

In addition to pain, NK-1 antagonists are especially preferred in the treatment and prevention of urinary incontinence; irritative symptoms of benign prostatic hypertrophy; motility disorders of the gastrointestinal tract, such as irritable bowel syndrome; acute and chronic obstructive airway diseases, such as bronchospasm, bronchopneumonia, asthma, and adult respiratory distress syndrome; artherosclerosis; inflammatory conditions, such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, osteoarthritis, neurogenic inflammation, allergies, rhinitis, cough, dermatitis, urticaria, psoriasis, conjunctivitis, emesis, irritation-induced miosis; tissue transplant rejection; plasma extravasation resulting from cytokine chemotherapy and the like; spinal cord trauma; stroke; cerebral stroke (ischemia); Alzheimer's disease; Parkinson's disease; multiple sclerosis; amyotrophic lateral sclerosis; schizophrenia; anxiety; and depression.

NK-2 antagonists are especially preferred in the treatment of urinary incontinence, bronchospasm, asthma, adult respiratory distress syndrome, motility disorders of the gastrointestinal tract, such as irritable bowel syndrome, and pain.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also includes pharmaceutical compositions which contain, as the active ingredient, the compounds of Formula I associated with pharmaceutically acceptable carriers. In making the compositions of the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration

throughout the day.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added

to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Capsules, each containing 15 mg of medicament, are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg

Continuation of the Table on the next page

(continued)

Ingredient	Quantity (mg/capsule)
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

Formulation Example 9

An intravenous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	250.0 mg
Isotonic saline	1000 ml

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

Ingredient	Quantity Per Tablet
Active Ingredient	10.0 mg
Glycerol	210.5 mg
Water	143.0 mg
Sodium Citrate	4.5 mg
Polyvinyl Alcohol	26.5 mg
Polyvinylpyrrolidone	15.5 mg
Total	410.0 mg

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by refemce.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: ELI LILLY AND COMPANY
(B) STREET: Lilly Corporate Center
(C) CITY: Indianapolis
(D) STATE: Indiana
(E) COUNTRY: United States of America
(F) ZIP: 46285

(ii) TITLE OF INVENTION: 1-ARYL-2-ACETAMIDOPENTANONE DERIVATIVES FOR USE AS TACHYKININ RECEPTOR ANTAGONISTS

(iii) NUMBER OF SEQUENCES: 4

(iv) CORRESPONDENCE ADDRESS:
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(E) COUNTRY: United Kingdom
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: Macintosh
(C) OPERATING SYSTEM: Macintosh 7.0
(D) SOFTWARE: Microsoft Word 5.1

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: 95305084.6

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Phe Xaa Gly Leu Met
1 5

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met
1 5 10

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

His Lys Thr Asp Ser Phe Val Gly Leu Met
1 5 10

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

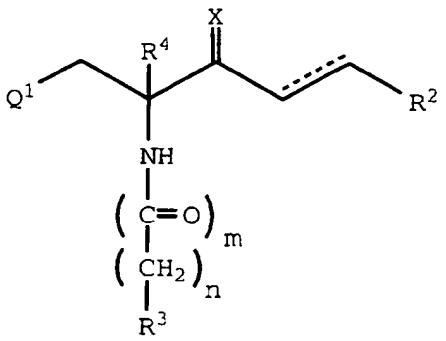
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Asp Met His Asp Phe Phe Val Gly Leu Met
1 5 10

Claims

1. A compound of the formula



wherein:

Q^1 is phenyl, naphthyl, indolyl, benzothienyl, benzofuranyl, benzyl, or fluorenyl, any one of which may be substituted with halo, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^4 is hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

X is =O, =NOH or =NO(C_1-C_6 alkyl);

the dotted line indicates an optional covalent bond;

m is 0 or 1;

n is 0-6;

R^3 is trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, hexamethyleneiminyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, tetrahydropyridinyl, reduced quinolinyl, reduced isoquinolinyl, phenyl-(C_1-C_6 alkylidenyl)-, phenyl-(C_1-C_4 alkoxy)-, quinolinyl-(C_1-C_6 alkylidenyl)-, isoquinolinyl-(C_1-C_6 alkylidenyl)-, reduced quinolinyl-(C_1-C_6 alkylidenyl)-, reduced isoquinolinyl-(C_1-C_6 alkylidenyl)-, benzoyl-(C_1-C_6 alkylidenyl)-, C_1-C_4 alkyl, or -NH-CH_2-R^5;

any one of which R^3 groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

or any one of which R^3 groups may be substituted with phenyl, piperazinyl, C_3-C_8 cycloalkyl, benzyl, C_1-C_4 alkyl, piperidinyl, pyridinyl, pyrimidinyl, C_2-C_6 alkanoylamino, pyrrolidinyl, C_2-C_6 alkanoyl, or C_1-C_4 alkoxycarbonyl;

any one of which groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, or C_2-C_4 alkanoylamino;

or R^3 is amino, a leaving group, hydrogen, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

R^2 is phenyl, phenyl-(C_1-C_6 alkylidenyl)-, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_1-C_8 alkyl, naphthyl, C_2-C_8 alkenyl, or hydrogen;

any one of which groups except hydrogen may be substituted with one or two halo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, nitro, trifluoromethyl, or C_1-C_3 alkyl groups; and

R^5 is pyridyl, anilino-(C_1-C_6 alkylidenyl)-, or anilinocarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound as claimed in **Claim 1** wherein R^2 is phenyl, or phenyl-(C_1-C_6 alkylidenyl)-, optionally substituted with one or two chloro, fluoro, trifluoromethyl, methoxy, ethoxy, methyl, or ethyl groups.

3. A compound as claimed in **Claim 2** wherein Q^1 is phenyl, 2-indolyl, 3-indolyl, 2-indolinyl, 3-indolinyl, or naphthyl optionally substituted with one or two chloro, fluoro, methyl, ethyl, methoxy, or ethoxy groups.

4. A compound as claimed in **Claim 3** wherein R^3 is phenyl, piperazinyl, piperidinyl, morpholinyl, benzofuranyl, phenyl-(C_1-C_4 alkylidenyl)-, phenyl-(C_1-C_4 alkoxy)-, -NH-CH_2-R^5, any one of which groups may be substituted.

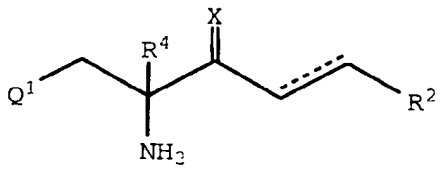
5. A compound as claimed in **Claim 4** wherein R^3 is 1-(4-phenyl)piperazinyl, 1-(4-cyclohexyl)piperazinyl, 1-(4-phenyl) piperidinyl, 1-(4-cyclohexyl)piperidinyl, 1-(4-isopropyl)piperazinyl, or 1-[4-(1-piperidinyl)]piperidinyl.

6. A pharmaceutical formulation comprising as an active ingredient a compound as claimed in any one of **Claims 1 to 5**, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

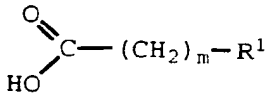
7. A compound as claimed in any one of **Claims 1 to 5** for use in the treatment or prevention of a physiological disorder

associated with an excess of tachykinins.

8. A process for preparing a compound as claimed in any one of **Claims 1 to 5** in which m is 1, which comprises reacting a compound of the formula



with a compound of the formula



or a salt or solvate thereof, optionally in the presence of an activating agent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 5084

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO-A-94 10167 (MERCK SHARP & DOHME ;LEWIS RICHARD THOMAS (GB); MACLEOD ANGUS MURR) 11 May 1994 see whole document, in particular pages 6, 7 and 9	1-8	C07D403/12 C07D401/12 A61K31/495 A61K31/445 C07D209/16 C07D307/81 C07D333/58
X	WO-A-94 01402 (MERCK SHARP & DOHME ;LEWIS RICHARD THOMAS (GB); MACLEOD ANGUS MURR) 20 January 1994 see whole document, in particular pages 3, 6 and 7	1-8	
X	WO-A-93 18023 (MERCK SHARP & DOHME) 16 September 1993 * the whole document *	1-8	
P,X	WO-A-94 19320 (MERCK SHARP & DOHME ;KELLEHER FINTAN (GB); LEWIS RICHARD THOMAS (G) 1 September 1994 * the whole document *	1-8	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	13 October 1995	Steendijk, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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